

Hypercoagulability in Pulmonary Hypertension



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KEYWORDS

- Pulmonary arterial hypertension • Hypercoagulability • Thromboembolism • Anticoagulation
- Pulmonary hypertension • Pulmonary embolism • Right heart failure • Right ventricle

KEY POINTS

- Patients with pulmonary arterial hypertension are at increased risk of developing thrombi.
- There are known and suspected pathways that contribute to the hypercoagulability in patients with pulmonary arterial hypertension.
- The benefit of anticoagulation and antiplatelet therapy is not known in this patient population.
- Hypercoagulability is an etiology and a consequence of pulmonary hypertension.

INTRODUCTION

Pulmonary hypertension (PH) is defined as increased pressure in the pulmonary circulation, defined by convention and consensus as a mean pulmonary artery pressure of at least 25 mm Hg at rest.¹ The World Health Organization (WHO) has classified PH into 5 major groups: pulmonary arterial hypertension (PAH), PH caused by left heart disease, PH caused by lung disease or chronic hypoxia, PH caused by chronic thromboembolic disease, and a miscellaneous group.^{2,3} PAH is a clinical condition that falls under WHO group 1, and can be idiopathic (IPAH), heritable (HPAH), caused by drugs and toxins (DTPAH), or associated with several other conditions (APAH) including connective tissue disease, congenital heart disease, HIV infection, or portal hypertension. PAH is characterized by molecular and pathologic alterations in the pulmonary circulation that result primarily in progressive vascular remodeling of the pulmonary arteries, increased pulmonary vascular resistance, and eventually right heart failure and death.^{4,5} These alterations

are caused by several inflammatory, metabolic, and cellular changes that ultimately result in occlusive lesions, in situ thromboses, and plexiform lesions, that are all representative of the pathologic findings of PAH.^{4,6,7} There is evidence of pro-thrombotic pathobiology which suggests an increased hypercoagulable state in PAH patients. Based on limited evidence, anticoagulation therapy is recommended in certain PH patients; however, the degree of hypercoagulability and benefit of anticoagulant therapy are not known.

PATHOPHYSIOLOGY OF PULMONARY ARTERIAL HYPERTENSION

PAH is characterized by excessive vasoconstriction of the distal pulmonary arteries (although the vasculopathy is not strictly limited to the pulmonary arterial system⁸). This is related to endothelial dysfunction and smooth muscle cell hypertrophy and proliferation (that at least in part is related to abnormal function or expression of potassium channels on smooth muscle cells), which leads to impaired production of vasodilator and

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antiproliferative agents such as nitric oxide and prostacyclin, as well as overexpression of vasoconstrictor and proliferative substances such as thromboxane A2 and endothelin-1.⁵ Other pathways and molecules, including serotonin,⁹ have also been implicated in the pathogenesis of PAH. Activation of the endothelin pathway has been demonstrated in both plasma and lung tissue of PAH patients.¹⁰ Although it is unclear whether increased endothelin-1 is a cause or consequence of PAH, it is known that endothelin-1 causes vasoconstrictive and mitogenic effects by binding to pulmonary vascular smooth muscle cells.¹¹ Endothelin receptor antagonists are efficacious in improving symptoms, exercise capacity, hemodynamics, and time to clinical worsening in PAH patients.^{12,13}

The nitric oxide and cyclic guanosine monophosphate (cGMP) pathway is also important in the pathogenesis of PAH. Inhibition of cGMP destruction by phosphodiesterase type 5 (PDE-5) inhibitors results in pulmonary vasodilation. PDE-5 inhibitors also have antiproliferative effects.¹⁴ PDE-5 inhibitors and guanylate cyclase stimulators are approved for the treatment of PAH and have shown to varying degrees benefits in hemodynamics, exercise capacity, and time to clinical worsening as with endothelin receptor antagonists.^{2,15}

The third pathway that has been a major therapeutic target for PAH is the prostacyclin pathway. Prostacyclin is predominantly produced by endothelial cells, and it induces potent vasodilation. It also inhibits platelet aggregation, and has cytoprotective and antiproliferative effects.¹⁶ PAH patients have a reduction in prostacyclin synthase expression in pulmonary arteries and prostacyclin urinary metabolites.¹⁷ Synthetic analogs of prostacyclins have been developed that share similar pharmacodynamic effects of prostacyclin.^{18–20} Efficacy of prostanoids is also seen in APAH and CTEPH (although currently not approved for CTEPH).^{21–23}

A common feature in all forms of PAH is the vascular remodeling of the distal region of pulmonary arteries. This pathologic remodeling results in the formation of a layer of myofibroblasts and extracellular matrix between the endothelium and the internal elastic lamina, termed the neointima. The cellular processes underlying the muscularization of the usually nonmuscular distal arteries is incompletely understood, but the adventitial fibroblast is thought to be the first cell activated to proliferate and synthesize matrix proteins in response to a pulmonary hypertensive stimulus.²⁴ Upregulation of matrix metalloproteinases occurs, and these metalloproteinases are involved in the migration of the adventitial fibroblasts into the

media layer. PAH is also associated with alterations of proliferation and apoptosis, resulting in thickened and obstructive pulmonary arteries.⁵

Endothelial cells also play a key role in vascular remodeling. Disorganized endothelial cell proliferation leads to the formation of plexiform lesions that are characteristic of PAH. The initiating stimulus that results in abnormal endothelial proliferation is not known, but may be hypoxia, shear stress, inflammation, response to drug or toxin, or a combination of these with a background genetic/genomic susceptibility. Defects in growth-suppressive genes have been reported in plexiform lesions, including growth factors such as platelet-derived growth factor, fibroblast growth factor, transforming growth factor beta (TGF β), and bone morphogenic proteins.^{2,25}

Inflammation also contributes to the pathogenesis of PAH. Pathologic specimens of patients with PAH show an accumulation of perivascular inflammatory cells including macrophages, dendritic cells, T and B lymphocytes, and mast cells. There is also an increased level of circulating cytokines and chemokines.^{26–28} The role of inflammation is particularly noted in certain groups of PAH including HIV APAH and connective tissue disease APAH. Interestingly, patients with systemic lupus erythematosus APAH have improved on immunosuppressive therapy, emphasizing the role of inflammation in this subset of patients.^{29–31} The pathogenesis of PH in patients with sickle cell disease (WHO group 5 PH) is also linked to inflammation, as elevated inflammatory markers and levels of cytokines and chemokines are associated with worse hemodynamics and poorer clinical outcomes.^{32,33} Mitochondrial dysfunction has also been shown to be pathologic in PAH.³⁴

Pathologically, PAH results in medial hypertrophy, intimal proliferative and fibrotic changes, adventitial thickening, plexiform lesions, and thrombotic lesions in the distal pulmonary arteries. Thrombi are present in both the small distal pulmonary arteries and in proximal elastic pulmonary arteries.²

HYPERCOAGULABILITY IN PULMONARY ARTERIAL HYPERTENSION

There is a high prevalence of vascular thrombotic lesions found postmortem in patients with IPAH, as described in several studies.^{35–38} These *in situ* thromboses may be caused by abnormalities in the coagulation cascade, endothelial cells, and/or platelets. Reduced plasma fibrinolysis was first reported in 1973.³⁹ Since then, studies have shown that PAH patients have elevated plasma levels of fibrinopeptide A- and D-dimers,⁵ and 1 study found

increased levels of fibrinogen and decreased fibrinolytic response in patients with IPAH, comparable to that of patients with CTEPH.⁴⁰ Fibrinopeptide A is generated when thrombin cleaves fibrinogen, suggesting an elevated level of plasma thrombin activity, and indeed studies have shown increased thrombin activity in treatment-naïve PAH patients.⁴¹

Procoagulant activity and fibrinolytic function of the pulmonary artery endothelium are also altered. This dysfunction is reflected by the increased levels of von Willebrand factor and plasminogen activator inhibitor type-1 in the plasma of PAH patients. Plasminogen activator inhibitor was found in much higher concentrations in arterial blood than in mixed venous blood, suggesting intrapulmonary production.⁴² Additionally, shear stress of blood flow toward vessel walls generates a thrombogenic surface, resulting in thrombotic lesions. The effect of shear stress and vessel injury can be seen in other types of PH as well, suggesting that the prothrombotic state is not unique to PAH.⁵

Tissue factor is a transmembrane glycoprotein that initiates the coagulation cascade, and it is thought to play a role in angiogenesis and cancer metastasis.^{43–45} Tissue factor binds to factor VII to catalyze the activation of factor X, leading to the generation of thrombin and the formation of a fibrin clot. Tissue factor expression is sensitive to changes in blood flow, hypoxia, growth factors such as platelet-derived growth factor, and chemokines. One study found that tissue factor was upregulated in the diseased vessels of PAH patients.⁴⁶ Another study found tissue factor-expressing endothelial microparticles in the circulation of PAH patients.⁴⁷ Tissue factor expression may be a key contributor to the formation of *in situ* thromboses.

There is growing evidence that the interaction between platelets, and the arterial wall may contribute to functional and structural alterations in the pulmonary vessels. Apart from their known role in coagulation, platelets release procoagulant, vasoactive, and mitogenic mediators in response to vascular abnormalities, such as thromboxane A₂, platelet-activating factor, serotonin, platelet-derived growth factor, TGF β , and VEGF.^{9,35,40} Thromboxane A₂, which stimulates the activation of new platelets and increases platelet aggregation, is increased in PAH patients, with a corresponding reduction in prostacyclin metabolites.⁴⁸ Abnormal platelet aggregation has been described *in vitro*, *in vivo*, and in human studies.^{49–51} PAH patients have higher levels of megakaryocyte-stimulating hormone thrombopoietin, and 1 study found that the pulmonary vasculature seemed to

be the site of production of thrombopoietin.⁵² Increased platelet production, activation, and aggregation may lead to a vicious cycle that contributes to thrombosis (Fig. 1). It is unclear whether thrombosis and platelet dysfunction are causes or consequences of PAH; however, the overarching evidence seems to be pointing toward an underlying pathology of hypercoagulability as a contributing etiology to PAH, and it gets worse as PAH and right heart dysfunction ensue.

In addition to the previously mentioned pathophysiologic abnormalities, patients with PAH may also be at increased risk for venous thromboembolism (VTE). PAH can cause significant dyspnea with exertion, and right heart failure can result in peripheral edema, both of which can lead a patient to be immobile.² Additionally, heart failure alone is an independent risk factor for VTE.⁵³

CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

CTEPH results from the chronic obstruction of pulmonary arteries due to thromboembolic disease. Usually, acute pulmonary emboli are resorbed by local fibrinolysis, with complete restoration of the pulmonary arterial bed.⁵⁴ CTEPH arises when prior acute pulmonary emboli for unknown reasons do not completely resorb. These unresolved clots then undergo fibrosis into an organized clot, ultimately leading to mechanical obstruction of the pulmonary arteries.^{2,54} This obstruction causes the release of inflammatory and vasculotropic mediators, resulting in vascular remodeling. Microvascular disease is also thought to occur, which can be related to shear stress in nonobstructed areas, postcapillary remodeling related to bronchial-to-pulmonary venous shunting, pressure, and inflammation.⁵⁴ Low blood flow states are created as a result of obstructed arteries and can result in the *in situ* thromboses, related to those of PAH. Thrombophilic factors such as antiphospholipid antibodies, lupus anticoagulant, protein S and C deficiency, activated protein C resistance including factor V Leiden mutation, prothrombin gene mutation, antithrombin III deficiency, and elevated factor VIII have been statistically associated with approximately one-third of CTEPH patients.² Obstruction of pulmonary arteries and secondary remodeling of small, peripheral pulmonary vessels most likely contribute to elevated total pulmonary resistance.^{8,55–57}

Pathologically, organized thrombi are tightly attached to the medial layer in the elastic pulmonary arteries, and subsequently replace normal intima. The thrombi occlude the lumen or form different grades of stenosis, webs, and/or bands.

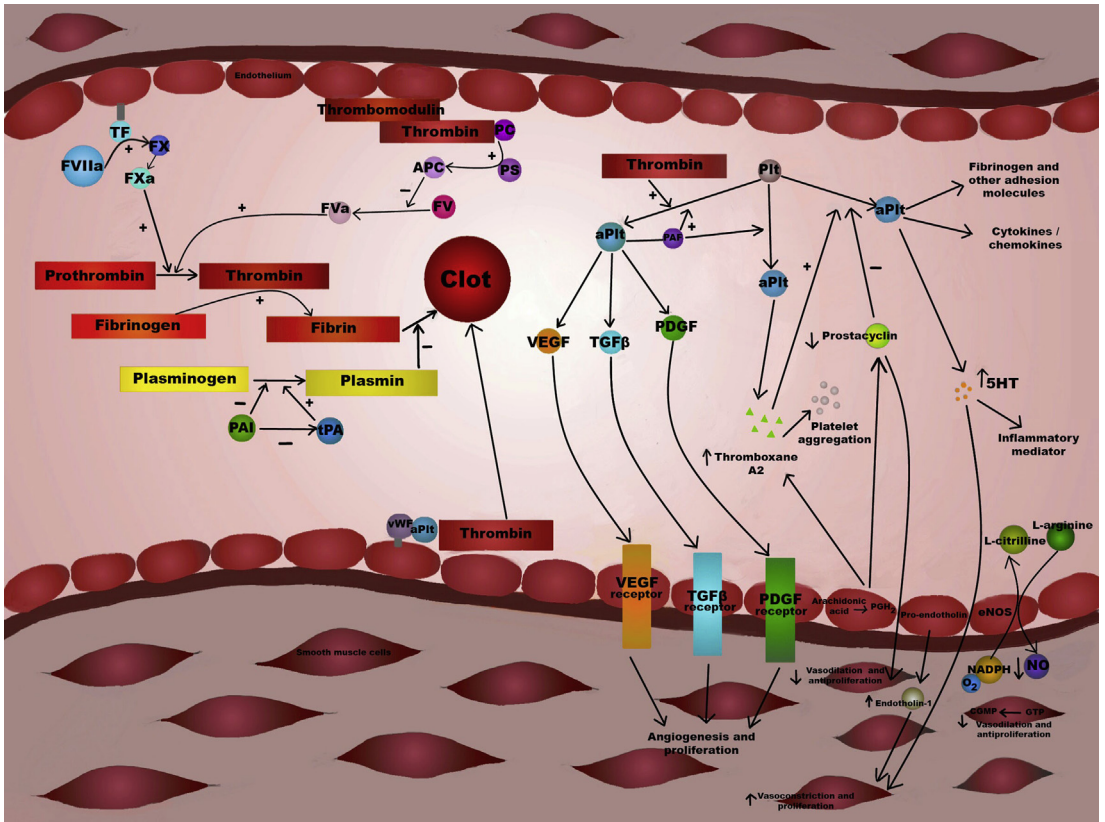


Fig. 1. Summary of hypercoagulable pathways in pulmonary arterial hypertension. This figure depicts a schematic of the pulmonary artery, with the combined known and suspected pathways that contribute to hypercoagulability in PAH. This figure is not comprehensive or inclusive of all known hypercoagulability pathways implicated in PAH. A condensed version of the coagulation cascade is shown, and in PAH, tissue factor (TF) is increased, resulting in increased thrombin, fibrin, and formation of clot. Plasminogen activator inhibitor (PAI) is also increased, decreasing clot inhibitors. Decreased thrombomodulin reduces inhibition of the clot formation. There are also more activated platelets in patients with PAH, and the effects of activated platelets are shown, including increased inflammatory mediators, vasoconstriction, platelet aggregation and prothrombotic factors, fibrinogen, and other adhesion molecules. Activated platelets stimulate growth factors, resulting in proliferation and angiogenesis. Finally, the prostacyclin, endothelin-1, and nitric oxide pathways are shown, highlighting their differential effects on vasoconstriction and proliferation, and are the primary targets of the currently available treatments for PAH. 5HT, serotonin; APC, activated protein C; aPlt, activated platelet; cGMP, cyclic guanosine monophosphate; eNOS, endothelial nitric oxide synthase; FV, factor V; FVa, activated factor V; FVIIa, activated factor VII; FX, factor X; FXa, activated factor X; GTP, guanosine triphosphate; NADPH, nicotinamide adenine dinucleotide phosphate hydrogenase; O₂, oxygen; PAI, plasminogen activator inhibitor; PC, protein C; PDGF, platelet-derived growth factor; PGH₂, prostaglandin H₂; Plt, platelet; PS, protein S; TF, tissue factor; TGFβ, transforming growth factor β; tPA, tissue plasminogen activator; VEGF, vascular endothelial growth factor; vWF, von Willebrand factor.

Collateral vessels from the systemic circulation (bronchial, costal, diaphragmatic, and coronary arteries) can grow to attempt reperfusion of areas distal to the obstructed territories. The microvascular changes that occur in occluded and nonoccluded areas are similar to those seen in PAH, although plexiform lesions are uncommon.^{2,58}

It is estimated that 1% to 4% of acute pulmonary embolism survivors develop CTEPH within 2 years from their first embolic event.^{55,59,60}

Anywhere from 25% to 50% of CTEPH patients do not have a past medical history of pulmonary embolism or deep vein thrombosis.^{55,61} It is suspected that thrombotic and/or inflammatory lesions exist in the pulmonary vasculature, resulting in the formation of thromboses and vascular remodeling without a clinically evident acute thromboembolic event. Conditions that cause chronic inflammatory states such as myeloproliferative disorders and inflammatory bowel disease

and postsplenectomy patients have been associated with the development of CTEPH.⁶² Unlike all other forms of PH, patients with CTEPH are potentially curable via a pulmonary endarterectomy.⁶³ The feasibility and success of this surgery depend on the surgical accessibility of thromboembolic residues and the underlying comorbidities of the patient.^{63,64} However, even with successful removal of chronic clots, some patients continue to have PH postoperatively. It is speculated that persistent PH is partly due to the remodeled microvasculature.⁵⁸ Balloon pulmonary angioplasty has also been gaining momentum in CTEPH management; however, its exact role is yet to be determined, as its technique, strategy, and catheters are rapidly evolving.⁶⁵

ANTICOAGULATION AND PULMONARY HYPERTENSION

Currently, anticoagulation is recommended for patients with IPAH, HPAH, and DTPAH. According to the 2015 European Society of Cardiology and the European Respiratory Society guidelines, anticoagulation is a class IIb recommendation, meaning that its usefulness and efficacy are not well established, but it may be considered (Table 1).² There have been some retrospective and observational single-center studies that have shown survival benefit in patients who get anticoagulation with warfarin.^{36,66} These early studies were done prior to the available PAH-targeted therapies.^{36,66–68} More recent randomized control trials and registry data have been inconclusive. For example, in 2014, the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) registry examined the survival rates of PAH patients based on use of anticoagulation. It found that in the subgroup of IPAH patients, there was a significant improvement in 3-year survival.⁶⁹ A major caveat to the COMPERA registry is that the median age of this population receiving anticoagulation was 70 years, and it does not reflect the typical demographics of the PAH population.

In contrast, the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) compared the survival of IPAH patients on warfarin with those who have never been anticoagulated, and found no difference in survival.⁷⁰ These limited and inconclusive data likely reflect the heterogeneity of PAH patients. Clinical use of anticoagulation in IPAH patients is widely variable and provider dependent. It is generally recommended that in the absence of contraindications, patients on long-term intravenous prostanoid analogues

Table 1
Summary of evidence for anticoagulation by World Health Organization groups

	WHO Group	Class of Recommendation ^a
1	PAH	IIb
	IPAH	IIb
	HPAH	IIb
	DTPAH	IIb
	CTD-PAH	III
	Porto-PH	III
	HIV-PAH	Unknown
	CHD-PAH	Unknown
2	PH caused by left heart disease	Unknown
3	PH caused by lung disease/chronic hypoxia	Unknown
4	CTEPH	I
5	Miscellaneous	Unknown

Abbreviations: CHD-PAH, congenital heart disease-pulmonary arterial hypertension; CTD-PAH, connective tissue disease-pulmonary arterial hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; DTPAH, drugs/toxins induced pulmonary arterial hypertension; HIV-PAH, HIV-induced pulmonary arterial hypertension; HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; PH, pulmonary hypertension; porto-PH, portopulmonary hypertension.

^a Class of recommendation. Class I recommendation: is recommended/indicated (evidence and/or general agreement that a given treatment of procedure is beneficial, useful, effective). Class IIa recommendation: should be considered (conflicting evidence with weight of evidence/opinion in favor of usefulness/efficacy). Class IIb: may be considered (conflicting evidence with usefulness/efficacy less well established). Class III: is not recommended (evidence or general agreement that given treatment is not useful/effective, and in some cases may be harmful).

Data from Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. The joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2015;37(1):67–119.

should receive anticoagulation therapy because of the risk of catheter-associated thrombosis.²

The potential benefits of anticoagulation for patients with APAH is even less clear. A subgroup analysis of from the REVEAL registry found that patients with systemic sclerosis APAH had an increased mortality when treated with warfarin.⁷⁰ The COMPERA registry also found to have other forms of APAH including those associated with connective tissue diseases, congenital heart disease, and portopulmonary hypertension, had no

survival benefit with anticoagulation.⁶⁹ Specific to congenital heart disease APAH, the use of anticoagulation in patients with Eisenmenger syndrome is controversial. These patients have a high incidence of pulmonary artery thrombosis and stroke, but also have an elevated risk of hemorrhage and hemoptysis.⁷¹ Although there are no data to guide this clinical dilemma, the authors' own practice is to avoid anticoagulation in congenital heart disease APAH. Hemoptysis is also a known complication of patients with IPAH and CTEPH, with prevalence varying from 1% to 6%,⁷² and it can limit the use of anticoagulation. Because many patients with portopulmonary hypertension have coagulopathy and thrombocytopenia, they have an elevated bleeding risk; anticoagulation is not recommended in these patients, although it has not been studied.

The preferred treatment for patients with CTEPH, as mentioned previously, is a pulmonary endarterectomy. Supplemental medical therapy for CTEPH includes anticoagulation, as well as diuretics and supplemental oxygen if needed for heart failure or hypoxemia, respectively. Although there are no studies comparing indefinite anticoagulation to no therapy or a shorter duration of anticoagulation, data extrapolated from treatment of acute and recurrent venous thromboembolism have led to the recommendation of lifelong anticoagulation for CTEPH patients, even after successful surgical intervention. The placement of routine inferior vena cava filter placement in this patient population is not justified by evidence.²

The role of direct oral anticoagulants (DOACs) for any group of PH is unknown. Several studies have shown that DOACs are at least as effective as warfarin for the management of venous thromboembolism and atrial fibrillation, and some have shown a reduction in bleeding and mortality.^{73,74} DOACs have not yet been studied in people with PAH, but in a monocrotaline-induced PAH rat model, rivaroxaban attenuated the increase in right ventricular systolic pressure and right ventricular hypertrophy caused by monocrotaline.⁷⁵ Although the generalizability of this to people is limited, it does warrant further investigation into the role of DOACs in PAH.

Since dysregulated platelets have been identified in the pathophysiology of PAH, antiplatelet therapy has been studied. However, although some studies have shown reduction in thromboxane A2 levels and reduction in platelet activation markers with aspirin, none have shown any improvement in exercise tolerance.^{76,77} These studies are small, and it is possible that larger studies or the investigation of newer antiplatelet agents may identify a role for platelet inhibitors in

the treatment of PAH. It is worth noting, however, that many of the PAH medications, as mentioned previously, do have antiplatelet effects.^{50,78}

SUMMARY

Given how heterogeneous the etiologies and pathophysiology are for each WHO group of PH, it is no surprise that the degree of hypercoagulability and benefit of anticoagulation would be variable between groups and subtypes. CTEPH is usually caused by an initial acute venous thromboembolism and has been associated with thrombophilic disorders; anticoagulation has a clear benefit in these patients. There is pathophysiological evidence that PAH is a prothrombotic state caused by the dysregulation of coagulation, fibrinolysis, and endothelial cells. These abnormalities, combined with in situ thromboses found in pulmonary arteries, argue that PAH patients are in a hypercoagulable state and may benefit from anticoagulation therapy. Studies investigating the benefit of anticoagulation in IPAH patients have yielded mixed results. Each individual subtype of APAH will need to be further investigated to assess the benefit of anticoagulation. Given that an increased bleeding risk limits the use of anticoagulation even in patients who would derive benefit, further study of DOACs and antiplatelet agents is also overdue.

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